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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,698	08/02/2005	Andre Francois Gorenflot	2002.010 US	2601

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PATENT DEPARTMENT
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EXAMINER	
GANGLE, BRIAN J	

ART UNIT	PAPER NUMBER
1645	

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04/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,698	GORENFLOT ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,23-26 and 29-39* is/are pending in the application.

4a) Of the above claim(s) *32-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15, 23-26, and 29-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/17/2008 has been entered.

The amendment and remarks, filed 1/17/2008, are acknowledged. Claims 24-26, 29, and 31 are amended. Claims 15, 23-26, and 29-39 are pending. Claims 32-39 are withdrawn as being drawn to non-elected inventions. Claims 15, 23-26, and 29-31 are currently under examination.

Objections Withdrawn

The objection to the specification because the title of the invention is not descriptive is withdrawn in light of applicant's amendment thereto.

New Objections

Claims 25-26 are objected to because of the following informalities: the claims should recite "further comprising" rather than "comprising." Appropriate correction is required.

Claim Rejections Withdrawn

The rejection of claims 24-26 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in light of applicant's amendment thereto.

The rejection of claims 24-26 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of preparing a vaccine against *Babesia divergens*, comprising mixing a immunogenic composition comprising a saponin adjuvant and a fusion protein comprising a *Babesia* Bd37 polypeptide and a decay accelerating factor peptide with a saponin and a pharmaceutically acceptable carrier, does not reasonably provide enablement for the claims as drawn, is withdrawn in light of applicant's amendment thereto.

The rejection of claims 29 and 31 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling because the amino acid sequence of the *Babesia* BD37 polypeptide which is associated with NCBI accession number CAD19563 is critical or essential to the practice of the invention, but not included in the claim(s), is withdrawn in light of applicant's amendment thereto.

The rejection of claims 24-26 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the phrase "preparing a vaccine," is withdrawn in light of applicant's amendment thereto.

The rejection of claim 25 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the phrase "wherein at least one additional immunoactive component is combined with said vaccine," is withdrawn in light of applicant's amendment thereto.

The rejection of claim 26 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the phrase "wherein said vaccine is freeze-dried," is withdrawn in light of applicant's amendment thereto.

The rejection of claims 29 and 31 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the terms "NCBI accession no. CAD19563," is withdrawn in light of applicant's amendment thereto.

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 15, 23-26, and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caras (WO 89/01041, 1989, IDS filed 1/7/2005) in view of Carcy *et al.*

(Infect. Immun., 63:811-817, 1995, IDS filed 1/7/2005) and Gupta *et al.* (Vaccine, 13:1263-1276, 1995), is maintained for the reasons set forth in the previous office action.

Applicant argues:

1. That the present application explains the difficulties in using saponins as adjuvants in vaccines and that the instant invention allows the use of saponins in a low enough concentration to avoid adverse local reactions.

2. That Caras does not mention saponins; and while Carcy uses Bd37 with Quil A, they do not suggest reducing the Quil A concentration; and that Gupta merely provides a general description of the use of saponins. Applicant asserts that "none of these publications comes up with the idea of fusing a core protein with a hydrophobic peptide, in order to be able to reduce saponin concentrations to reduce local and toxic reaction, while maintaining a high enough immunogenicity level." Applicant further asserts that there is no connection between the references that would lead a skilled person to solve the problem of saponin toxicity versus reduced immunogenicity upon lowering the saponin concentration.

3. That the examiner has used improper hindsight reasoning in combining the references. Applicant argues that nothing in the Caras reference would lead the skilled artisan to select the claimed Bd37 peptide as part of the fusion protein.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, those of skill in the art were well aware, at the time of invention, of the issues surrounding the use of saponins as adjuvants. Numerous references can be found describing the activity and use of saponins and the toxicity of saponins. There are also numerous references that have successfully used saponins, apparently without adverse effects (including in vaccines against *Babesia*), and saponins have been widely used in veterinary vaccines. Gupta was cited as an exemplary reference which discussed the use of saponins. However, this is hardly the only reference on the subject. Dalsgaard (Vet. Immunol. Immunopathol., 17:145-152, 1987) state that Quil A is used extensively in veterinary vaccines and state that since it has potent adjuvant activity in low doses, it is usually well tolerated in most veterinary vaccines (see page 149, paragraph 4). Dalsgaard describes the mechanism of Quil A activity and even finishese the section on saponins by suggesting the manipulation of poorly immunogenic peptides by altering their hydrophobicity (which is what the instant invention does) to create better vaccines (page

150, paragraph 3). Campbell *et al.* (Res. Immunol., 143:526-530, 1992) state that saponins have been found to be effective adjuvants for a variety of different antigens, and that, since toxicity need not be a limiting factor, they can be administered either parenterally or non-parenterally (page 529, final paragraph). Campbell *et al.* also show results from several studies where very low doses of saponins were used in vaccines without side effects (see Table 1). Edelhofer *et al.* (Parasitol. Res., 84:181-187, 1998), Schetters (EP 0691131B1, 1995), and Valentin *et al.* (Infect. Immun., 61:734-741, 1993) each used Quil A in combination with *Babesia* antigens. In fact, Valentin *et al.* showed that none of the vaccinated animals had local reactions to the vaccine (see page 737, column 2, paragraph 2). Clearly, the use of saponins and their advantages and disadvantages at various concentrations were very well known in the art before the instant application was filed.

Regarding argument 2, the examiner accepts that none of the cited publications discloses the claimed invention. However, the instant rejection was made under 35 USC 103, not 35 USC 102. It is the combination of references that renders the instantly claimed invention obvious. While applicant asserts that there is no connection between the references that would lead a skilled person to solve the problem of saponin toxicity versus reduced immunogenicity upon lowering the saponin concentration, applicant has not shown any evidence that there is a problem of saponin toxicity versus reduced immunogenicity upon lowering the saponin concentration. In fact, as stated above, the art (including applicant's own published work) shows that saponin toxicity is not generally an issue. Furthermore, there is nothing in the claims that requires reduced toxicity or a reduced concentration of saponins.

Regarding argument 3, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Applicant argues that nothing in the Caras reference would lead one to select Bd37 as the antigen in the fusion protein. This is true; Caras discloses fusion proteins containing DAF and any given antigen. However, Carcy specifically states that Bd37 appears to be a potential immunogen in a vaccine against babesiosis.

As outlined previously, the instant claims are drawn to methods of preparing an immunogenic composition comprising combining a saponin adjuvant in a free form with a fusion protein comprising a *Babesia* Bd37 polypeptide and a decay accelerating factor peptide (claim 15); wherein the saponin is Quillaja (claim 23); wherein a vaccine is made by combining said composition with a pharmaceutically acceptable carrier and the Bd37 polypeptide comprises the sequence of SEQ ID NO:20 (claim 24); wherein said vaccine comprises at least one additional immunoactive component (claim 25); wherein said vaccine is freeze-dried (claim 26); wherein the *Babesia* Bd37 polypeptide comprises the sequence of SEQ ID NO:20 (claims 29 and 31); and wherein the decay accelerating factor peptide comprises SEQ DI NO:14 (claims 30 and 31).

Caras discloses a fusion protein comprising decay accelerating factor and any chosen antigen (see page 15, lines 20-30). Said fusion protein contains SEQ ID NO:14 (see Figure 3) Caras also teaches that DAF proteins are generally stored after lyophilization (page 26, lines 30-35).

Caras differs from the instant claims in that the antigen in the fusion protein is not disclosed as Bd37 and no saponin adjuvant is included in the composition.

Carcy *et al.* disclose a polypeptide from *Babesia divergens* known as Bd37. Carcy *et al.* state that Bd37 appears to be a potential immunogen in a vaccine against babesiosis (see page 811, column 2, paragraph 1). According to the instant specification, the Bd37 polypeptide disclosed by Carcy *et al.* has the sequence of NCBI accession number CAD19563 (SEQ ID NO:20) (page 14, lines 25-35).

Gupta *et al.* disclose adjuvants including Quil A, which is widely used in veterinary vaccines (page 1271, column 1, paragraph 4). Quil A is a heterogeneous mixture of saponins (page 1271, column 1, paragraph 4). Gupta *et al.* also state that adjuvants help antigens to elicit an early, high, and long-lasting immune response with less antigen, thus saving on vaccine production costs (see abstract).

Therefore, it would have been obvious to the person of ordinary skill in the art, at the time of invention, to use Bd37 as the antigen in the fusion protein of Caras because Bd37 is a vaccine candidate antigen. One would also have been motivated to include a saponin adjuvant because adjuvants antigens to elicit an early, high, and long-lasting immune response with less antigen, thus saving on vaccine production costs. With regard to claim 25, Quil A contains

multiple saponins; therefore, a composition with Quil A would include a saponin and an additional immunoactive component (another saponin).

One would have had a reasonable expectation for success because Caras states that any antigen can be used in their fusion protein. In addition, Gupta *et al.* disclosed that Quil A has been widely used in veterinary vaccines.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian J Gangle/
Examiner, Art Unit 1645

/Shanon A. Foley/
Supervisory Patent Examiner, Art Unit 1645